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Original Article

Pulmonary benign metastasizing leiomyoma: clinical and therapeutic analyses of 11 patients treated at a single institution

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Abstract: Pulmonary benign metastasizing leiomyoma (BML) occurs predominantly in women of reproductive age and usually develops several years after the resection of uterine leiomyoma. There is no standardized treatment for pulmonary BML owing to its low incidence. In this study, we retrospectively analyzed 11 patients with pulmonary BML. Major symptoms, imaging findings, therapeutic modalities, and outcomes were analyzed. The median patient age was 51 years (range, 45-65 years). All patients had uterine leiomyoma, for which all but one patient received myomectomy or hysterectomy. The preoperative symptoms included chest pain and coughing in four (36.4%) patients. In eight (72.7%) patients, computed tomography can revealed bilateral, multiple pulmonary nodules. The interval between the surgery for uterine leiomyoma and the diagnosis of pulmonary BML ranged from 13 months to 19 years. Thoracoscopic wedge resection was performed for two patients with unilateral pulmonary tumors. Therapeutic modalities included bilateral salpingo-oophorectomy, gonadotropin-releasing hormone agonist, aromatase inhibitor, progestin, and tamoxifen. All but one patient is alive to date; the patient who received no treatment died of respiratory failure due to rapid progression of pulmonary BML. Our data for an unselected group of patients with pulmonary BML treated at a single institution are consistent with results from previous studies indicating that pulmonary BML is best managed with metastasectomy and/or a combination of surgery and hormonal therapy.

Keywords: Lung, benign metastasizing leiomyoma, uterus, leiomyoma, surgery, hormone therapy

Introduction

Uterine leiomyomas are the most common benign gynecological neoplasms in women of reproductive age. Rarely, it shows unusual growth patterns with extrauterine smooth muscle nodules that seem to be derived from a benign uterine leiomyoma. Metastasis commonly follows surgical treatment by myomectomy or hysterectomy for uterine leiomyomas [1]. Benign metastasizing leiomyoma (BML) is a very rare disease that has been reported in association with uterine leiomyoma. The term BML is used to describe the presence of benign smooth muscle tumors in an organ distant from the uterus [2]. Since Steiner's report in 1939 [3], approximately 90 cases of BML have been reported in the literature. However, a unified perspective has not emerged regarding the biological nature, pathogenesis, or prognosis of this disease, because nearly all previous studies were case reports. Furthermore, no standardized treatment has been established for BML.

The lungs are the most common site of metastasis for uterine leiomyoma, with characteristic scattered, bilateral nodules [4-6]. Data on the clinical behaviors, treatment, and patient outcomes for pulmonary BML are also rare. Even the necessity of surgery for this metastatic lesion remains controversial. In this report, we provide data on 11 patients with newly diagnosed pulmonary BML treated at a single insti-

Table 1. Antibodies used for immunohistochemical staining

Antibody	Source	Clone	Dilution
SMA	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	1A4	1:1,000
ER	Thermo Fisher Scientific Inc., Fremont, CA, USA	SP1	1:100
PR	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	PgR 636	1:50
TTF-1	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	8G7G3/1	1:100
Ki-67	Dako, Agilent Technologies, Inc., Carpinteria, CA, USA	MIB-1	1:50

SMA: smooth muscle actin; ER: estrogen receptor; PR: progesterone receptor; TTF-1: thyroid transcription factor-1.

tution over a 15-year period. We retrospectively analyzed the data in this series in order to determine significant clinical features that may affect the diagnosis and treatment of this disease.

Patients and methods

Patients and tissue specimens

We retrospectively analyzed all 11 patients who were consecutively diagnosed with histologically confirmed pulmonary BML and treated at the Samsung Medical Center between January 2000 and December 2014. Patient characteristics, including age, surgical treatment for uterine leiomyoma, respiratory symptoms, imaging findings, medical and/or surgical treatment for pulmonary BML, the presence of secondary metastasis to other organs, and follow-up period and outcome, were obtained through medical chart review. Surgical treatments for pulmonary BML included video-assisted thoracoscopic surgery (VATS) wedge resection or lobectomy of the lungs and bilateral salpingo-oophorectomy (BSO). Medical management included aromatase inhibitors (AI; anastrozole and letrozole), gonadotropin-releasing hormone agonists (GnRHa; triptorelin, leuprorelin, buserelin, and goserelin), progesterone, and selective estrogen receptor modulators (SERM; tamoxifen, raloxifene, and toremifene).

Histopathological examination

The resected specimens at the Samsung Medical Center were fixed in 10% neutral-buffered formalin and embedded in paraffin blocks. From each formalin-fixed, paraffin-embedded (FFPE) block, 4-μm sections were cut and stained with hematoxylin and eosin (H&E), and prepared for immunohistochemical staining. All H&E-stained slides were examined under routine light microscopy by gynecologic and pulmonary pathologists.

Immunohistochemistry

Immunohistochemical staining was performed on the FFPE tissue sections, using a Bond-maX automated immunostainer (Leica Biosystems, Melbourne, Australia) and a Bond Polymer Refined Detection Kit (Leica Biosystems). The details of the primary antibodies used are summarized in **Table 1**. Briefly, antigen retrieval was performed at 97°C for 20 min in ER1 or ER2 buffer. After blocking endogenous peroxidase activity with 3% hydrogen peroxide for 10 min, primary antibody incubation was performed for 15 min at room temperature. To verify antibody specificity, anti-mouse immunoglobulin was used instead of the primary antibody as a negative control.

Results

Clinical findings

Clinical characteristics and outcomes for the 11 patients with pulmonary BML are summarized in **Table 2**. The median patient age was 51 years (mean, 52.2; range, 45-65 years), with nine (81.8%) patients younger than 55 years of age. Three (27.3%) patients were postmenopausal. Seven (63.6%) patients did not have any respiratory symptoms. The major symptom was chest pain, occurring in three (27.2%) patients (Patients 1, 2, and 8). Other symptoms included a sensation of chest tightness (Patient 1), hemoptysis (Patient 2), cough (Patient 8), and fever (Patient 8). All but one patient (Patient 11) underwent surgery for uterine leiomyomas. Six (54.5%) and four (36.4%) patients received total hysterectomy and myomectomy, respectively. Eight (72.7%) patients had multiple, variable-sized leiomyomatous nodules in the uterus. The mean tumor size of the uterine leiomyoma was 5.4 cm (range, 2-16 cm). The interval between the surgery for uterine leiomyoma and the diagnosis of pulmonary BML ranged from 13 months to 19 years (mean, 8

Table 2. Clinical characteristics and outcomes of 11 patients with pulmonary BML

Patient No	Age	MP	Surgical Tx for UL	Interval between the Dx of UL and BML	Respiratory symptoms	CT findings	Surgical Tx for BML	Medical Tx for BML	Recurrence or secondary metastasis	F/U period after the Dx of BML	Current status
1	47	No	No	8 y 5 m	Chest pain and tightness	Unilateral, solitary nodule (2.0 cm)	VATS WR	No	No	2 y 1 m	NED
2	65	Yes	Hysterectomy	19 y	Chest pain and hemoptysis	Unilateral, multiple nodules	VATS WR and lobectomy	No	Pelvic wall	6 y 2 m	SD
3	48	No	Hysterectomy	2 y 5 m	Absent	Unilateral, solitary nodule (1.3 cm)	BSO	AI	No	4 m	SD
4	54	Yes	Hysterectomy	11 y	Absent	Bilateral, multiple nodules	BSO	AI	No	6 y 4 m	SD
5	45	No	Myomectomy	5 y	Absent	Bilateral, multiple nodules	BSO	GnRHa	No	3 y 2 m	SD
6	51	No	Hysterectomy	5 y	Absent	Bilateral, multiple nodules	BSO	AI and GnRHa	No	4 y	SD
7	53	No	Hysterectomy	11 y	Absent	Bilateral, multiple nodules	BSO	Progesterone	No	5 y 8 m	SD
8	59	Yes	Myomectomy	3 y 5 m	Cough and fever	Bilateral, multiple nodules	No	AI	No	1 y 2 m	SD
9	49	No	Myomectomy	1 y 1 m	Absent	Bilateral, multiple nodules	No	AI	No	3 y 10 m	SD
10	53	No	Hysterectomy	12 y	Absent	Bilateral, multiple nodules	No	SERM	No	4 y 11 m	SD
11	50	No	Myomectomy	8 y	Chest pain	Bilateral, multiple nodules	No	No	No	8 m	DOD

MP: menopause; Tx: treatment; UL: uterine leiomyoma; Dx: diagnosis; BML: benign metastasizing leiomyoma; y: year; m: month; CT: computed tomography; VATS: video-assisted thoracoscopic surgery; WR: wedge resection; BSO: bilateral salpingo-oophorectomy; AI: aromatase inhibitor; GnRHa: gonadotropin-releasing hormone agonist; SERM, selective estrogen receptor modulator; F/U: follow-up; NED: no evidence of disease; SD: stable disease; DOD: dead of tumor-related disease.

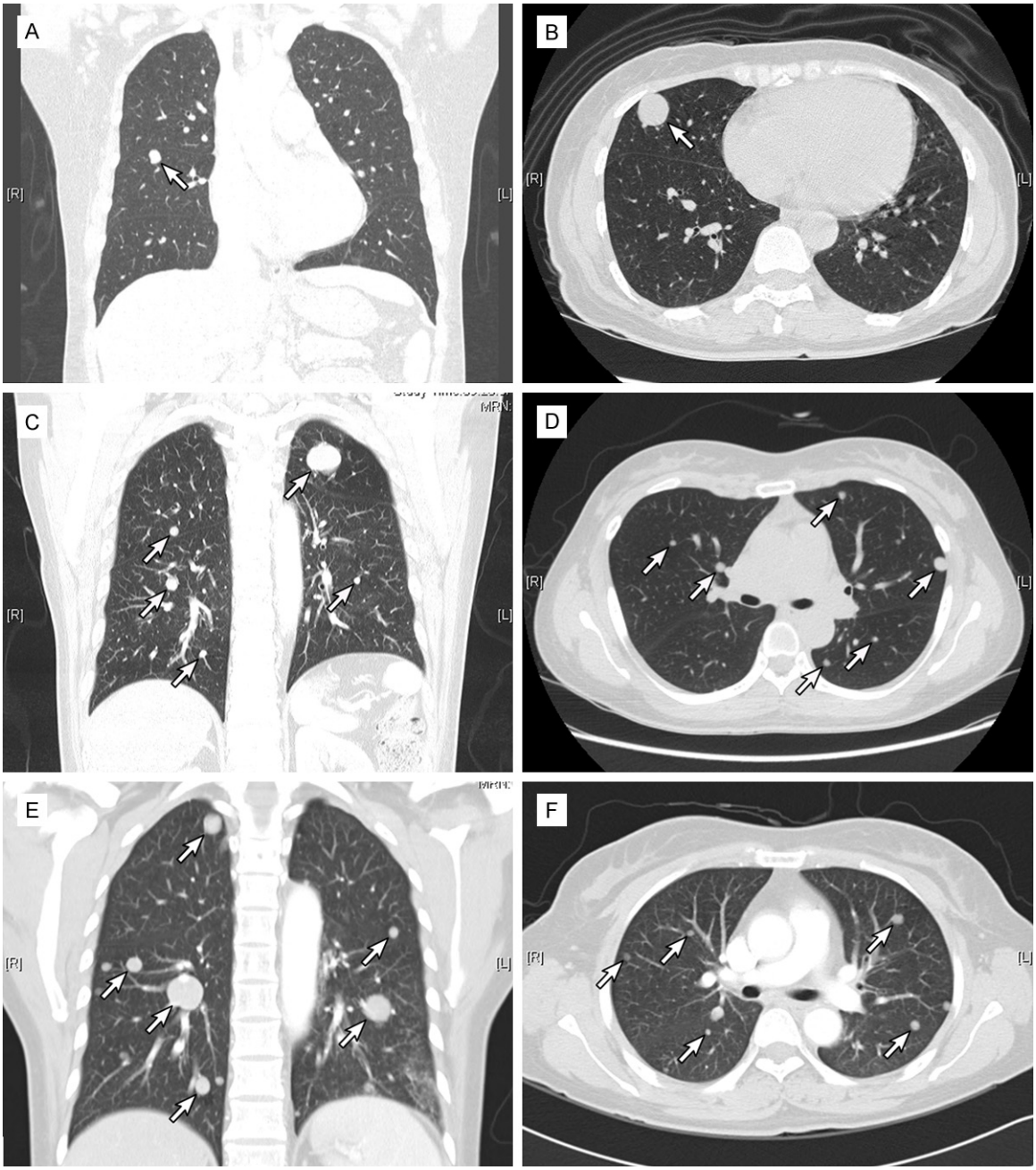

Figure 1. Imaging findings of pulmonary BML. (A) Patient 3. Chest CT reveals a 1.3-cm single, well-circumscribed nodule (white arrow) in the right middle lobe. (B) Patient 1. A 2.0-cm single, spherical nodular lesion (white arrow) is noted in the right middle lobe. (C-F) There are multiple, round, well-circumscribed and variable-sized nodules (white arrows) in both lungs. (C. Patient 5; D. Patient 7; E. Patient 8; F. Patient 10).

years; median, 8 years). Chest computed tomography (CT) was the primary diagnostic method and we found either single or multiple nodular lesions on the CT images of all patients. In two (18.1%) patients, CT revealed a single, spherical, well-circumscribed pulmonary nodule in the right middle lobe, measuring 1.3 cm (Patient 3; **Figure 1A**) and 2.0 cm (Patient 1; **Figure 1B**), respectively. Patient 2 had unilateral but multiple pulmonary nodules. The remaining eight (72.7%) patients had numerous, variable-sized pulmonary nodules, which were scattered throughout both lungs (**Figure 1C-F**). The pulmonary tumor size ranged from 0.6 cm to 8.0 cm (mean, 2.4 cm). In 10 (90.9%) patients, VATS biopsy was performed to con-

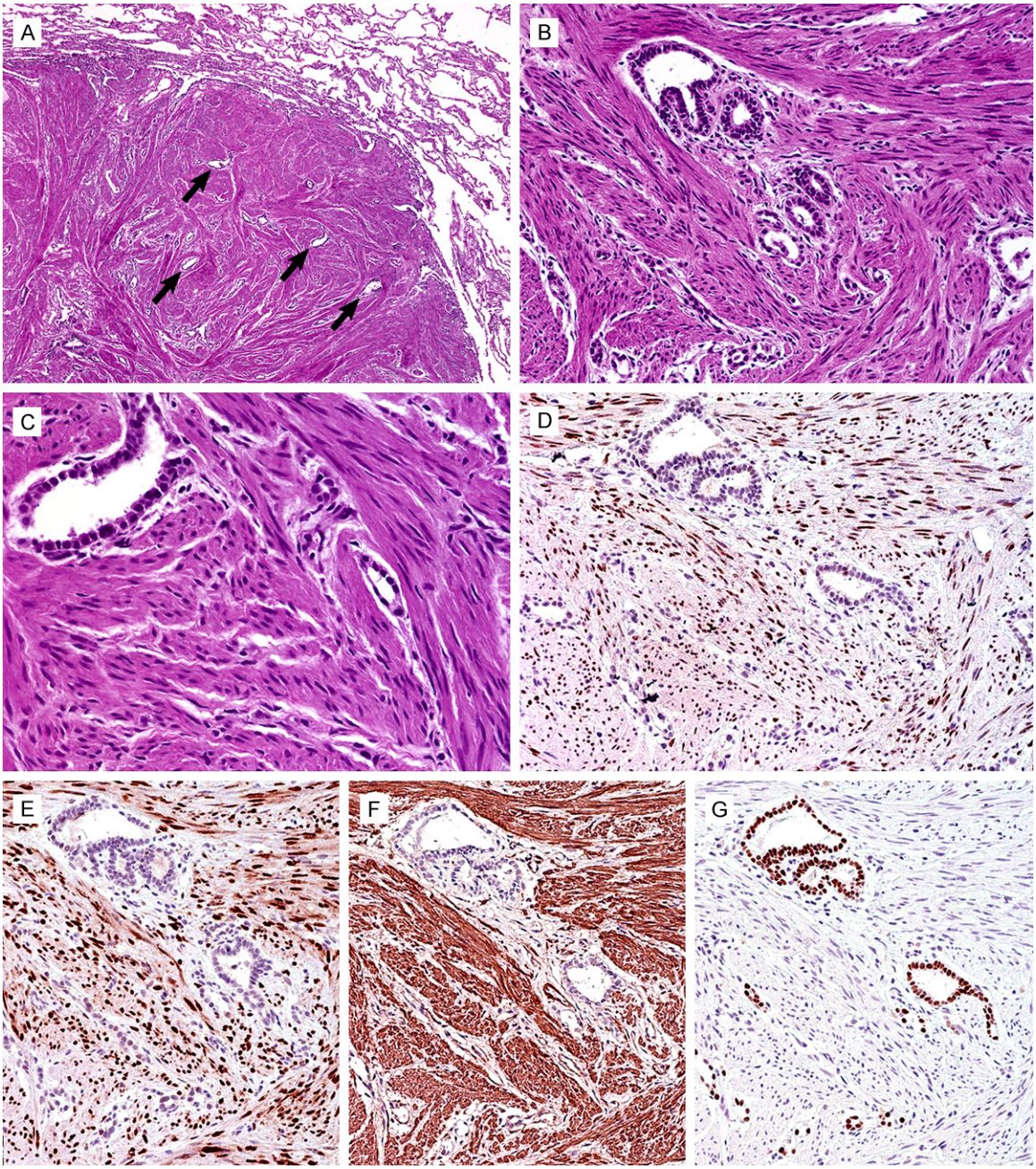

Figure 2. Representative H&E-stained sections (A-C) and immunohistochemical findings for pulmonary BML (D-G). (A) A well-circumscribed pulmonary tumor consists of abundant smooth muscle cells, which surround scattered glandular structures (black arrows). (B) The spindle-shaped smooth muscle cells are arranged in interlacing fascicles and whorls. The bronchial epithelial cells are entrapped within the tumor. (C) The smooth muscle cells display no cytologic atypia or mitotic figures. Immunohistochemically, strong nuclear positivity for (D) ER and (E) PR and cytoplasmic positivity for (F) SMA, together with (G) the absence of TTF-1 immunoreactivity, in the smooth muscle cells suggests that the tumor cells originated in the uterus. The entrapped bronchiolar epithelial cells serve as the internal control for TTF-1 immunostaining.

firm the diagnosis of BML histopathologically. The remaining patient was diagnosed with pulmonary BML by ultrasonography-guided percutaneous needle biopsy.

Two patients, one who had a single pulmonary nodule (Patient 1) and one with unilateral, multiple nodules (Patient 2), received VATS wedge resection and VATS wedge resection with lobec-

tomy, respectively. The tumor of Patient 2 was not removed completely, but no further treatment was performed. Patient 3 received BSO and AI therapy for a single lesion. Four (36.4%) of eight patients who developed bilateral, multiple pulmonary nodules received BSO and adjuvant medical treatment with AI, GnRHa, and/or progesterone, and three (27.3%) patients received AI or SERM only. The remaining patient (Patient 11) refused surgical resection or medical treatment for bilateral, multiple BML. Her disease rapidly progressed, and she died of respiratory failure due to extensive tumor involvement 8 months after the diagnosis of BML.

Clinical outcomes

Median follow-up was 46 months. One (9.1%) patient died during the study period (between 2000 and 2014). Nine (90.9%) patients were alive at the last follow-up and the presence of stable pulmonary lesions was monitored with sequential CT scans. In these patients, the size of the nodules decreased slightly during the medical treatment and no newly developed lesions were observed, and the disease status was evaluated as stable according to the "Response Evaluation Criteria In Solid Tumors" criteria. The remaining patient had no evidence of disease at the time of analysis. One patient developed recurrent leiomyoma in the pelvic wall after surgery but received no further treatment. No severe treatment complications were documented.

Histopathological findings

Histopathological examination of wedge-resected specimens revealed isolated, unencapsulated, solid nodules that were sharply demarcated from the adjacent pulmonary parenchyma (**Figure 2A**). The nodular surfaces appeared to be surrounded by alveolar epithelium. Entrapment of cleft-like and tubular spaces lined by cuboidal epithelium was noted in the interior of the nodules (**Figure 2B**). At high power, there was a proliferation of interlacing smooth muscle bundles without cytologic atypia (**Figure 2C**). Plump spindle-shaped smooth muscle cells with elongated nuclei and eosinophilic cytoplasm formed anastomosing fascicles. Lack of hypercellularity, moderate-to-severe cytologic atypia, atypical mitotic figures, and coagulative tumor cell necrosis excluded the possibility of metastatic leiomyosarcoma. There was no morphological evidence of diffuse growth or infiltration of small cells admixed with spiral arteriole-like vasculatures, excluding the possibility of metastatic endometrial stromal sarcoma.

Immunohistochemical findings

The tumor cells were strongly and diffusely positive for estrogen receptor (ER; **Figure 2D**), progesterone receptor (PR; **Figure 2E**) and smooth muscle actin (SMA; **Figure 2F**) in all patients. In contrast, thyroid transcription factor-1 (TTF-1) was present in entrapped bronchiolar epithelial cells only (**Figure 2G**). The Ki-67 labeling index was nearly negative (less than 1%) for the tumor cells, excluding the possibility of metastatic leiomyosarcoma or endometrial stromal sarcoma. In each patient, these morphologic features were the same as those of their previously resected uterine leiomyomas.

Discussion

Because of the rarity of BML, only a limited number of studies have investigated the disease; its risk factors, related etiology, and clinical behaviors have been poorly studied. However, the reported cases share common characteristics. Most included histories of prior uterine surgery, including myomectomy and hysterectomy, suggesting a clue to the pathogenesis of BML. While the lungs are known as the predominant metastatic site [7, 8], other sites, including skin, deep soft tissue, muscle, skull, spine and lymph nodes, have been reported [9-13]. The interval between surgical removal of the uterine leiomyoma and the discovery of extrauterine lesions is approximately 10 years on average [14, 15]. Consistent with previous data, we observed that 10 of 11 patients underwent uterine surgery and the mean interval between the surgery and the detection of pulmonary lesions was 8 years. However, pulmonary BML and uterine tumor are rarely discovered simultaneously, and it can be difficult to establish a diagnosis. Furthermore, if a patient has neither a previous history nor significant symptoms of gynecologic disease, it may be difficult to identify the primary origin of the pulmonary tumors.

BML mainly affects sexually mature women when hormonal effects are at a maximal level.

Most BMLs have been found to express ER and PR [12, 16]. Therefore, the lesions are generally recognized to be sex hormone responsive. Because of natural changes in hormonal levels after menopause, BMLs are rarely identified in postmenopausal women and are known to decrease in size after menopause. Only six cases of pulmonary BMLs in postmenopausal women have been reported in the literature [5, 7, 14, 15, 17, 18]. These studies reported that the postmenopausal women with pulmonary BMLs had no significant symptoms of respiratory disease. In contrast, we observed that two of three postmenopausal women with pulmonary BML had significant respiratory symptoms such as chest pain and coughing. However, the presence of respiratory symptoms was not associated with clinical status or outcome. In all patients reported previously, pulmonary lesions were detected several years after hysterectomy or myomectomy. In our series, the interval between the uterine surgery and the diagnosis of BML ranged from 41 months to 19 years.

There is no standardized treatment for BML because of the limited number of reported cases. Treatment options include surgical resection of pulmonary nodules, BSO and hormonal therapy. Some authors have stated that BSO should be considered as a primary treatment in premenopausal women [10, 19]. The authors of another study also suggested that resection should be undertaken whenever possible in patients with symptomatic metastasis [20]. In general, the presence or absence of ER and PR plays a key role in their management. Removal of estrogen stimulation by oophorectomy or hormonal therapy using a GnRHa, SERM, and AI has been suggested as the best option for unresectable metastatic lesions [12, 15, 21]. Clinical evidence of a hormonal influence is supported by the fact that the pulmonary nodules diminish in size following menopause, during pregnancy and after the withdrawal of hormonal contraception. In this study, surgical resection of pulmonary nodules, BSO, and hormonal therapy, as well as a combination of BSO and hormonal therapy, were effective in controlling BMLs. All but one patient remained stable for a median follow-up of 46 months after the initiation of therapy. Although this period might not be long enough to reach a definitive conclusion, taking into account the slow-growing nature of a BML, most patients with BML treated with either surgical or medical methods had good outcomes [1, 9-11]. Many authors support the idea that patients with BML are best managed with a combination of surgery for metastatic tumors and hormonal therapy [1, 9-11, 19, 20]. When the tumors are completely resected, no further treatment may be needed. In the event of incomplete surgery, it has been reported that hormonal therapy achieved good disease control.

However, not all patients seem to respond to hormone treatment [22], and side effects including flushes, fatigue, and nausea can be aggravating. One of our patients refused to undergo surgery or receive hormonal therapy because of menopausal symptoms. Consequently, she died of respiratory failure due to rapidly disseminated BML nodules filling up the entire lung parenchyma. A small proportion of BMLs have been reported to display an aggressive course [23]. A wait-and-see strategy appears inappropriate for BML. Depending on the extent and location of metastatic lesions and the hormonal receptor status, treatment should be individualized for each patient. It may be possible to discontinue hormonal treatment for some time if the tumors are well controlled. It also seems possible to restart these agents if the tumors begin to increase in size again. Importantly, a detailed examination and long-term follow-up period is recommended to avoid under- or overtreatment.

Histologically, pulmonary BML consists of benign smooth muscle cells that are similar to uterine leiomyoma. In our series, all of the tumors showed no evidence of high cellularity, epithelioid or symplastic patterns, vascular invasion, cytological atypia, coagulative tumor necrosis, or mitotic figures, excluding the possibility of malignancy. Their Ki-67 labeling index was very low, supporting the low proliferative state of these lesions. In addition, the pulmonary nodules contain glandular-appearing structures that comprise alveolar or bronchiolar epithelium, as observed on histopathology [24, 25]. These entrapped glandular elements are commonly observed in the interior of metastatic nodules, and can cause diagnostic confusion [15, 24, 25]. The lack of nuclear atypia and strong immunoreactivity for TTF-1 in the epithelial lining preclude the possibility of primary

lung cancer and metastatic malignancy. On radiographic examinations, the lung lesions are typically well-circumscribed, solitary, or multiple nodules ranging from a few millimeters to several centimeters in diameter scattered among normal interstitium [24]. They usually show little change and may even spontaneously regress [26]. Endobronchial and pleural sparing is characteristic [18]. A previous study reported that pulmonary BML presented as multiple nodules in 87% of cases (70% bilateral nodules and 17% unilateral nodules) or as a solitary nodule in 13% of cases [26]. Similarly, in our series, it presented in 81.8% of cases as multiple bilateral nodules, in 9.1% as multiple unilateral nodules and in 18.2% as a single nodule.

There is persisting controversy regarding the pathogenesis and biology of these lesions. Certain researchers hypothesize that BML, once termed 'multiple fibroleiomyomatous hamartoma', is a type of multiple smooth muscle *in situ* proliferation that is induced by estrogen and progesterone. The presence of entrapped epithelial elements contributed to this confusion. In contrast, others support the idea that BML results from the monoclonal, hematogenous spread of a differentiated uterine leiomyoma. Currently, the majority of studies concur with BML being a metastatic leiomyoma that metastasizes between the uterus and the lungs, as all reported cases are in women with a previous history of surgical resection for uterine leiomyoma. The patients with single pulmonary nodules or multiple nodular lesions of various sizes in both lungs reported in the present study had undergone myomectomy or hysterectomy, leading to the vascular spread of uterine smooth muscle cells. Hormone receptor positivity in extrauterine lesions and the response to hormone treatment also support this hypothesis. Another possible explanation is that the pulmonary lesions actually represent low-grade leiomyosarcomas of the uterus with metastatic potential [24]. However, the clinical course of BML is much less aggressive than a true leiomyosarcoma [12, 15]. Certain studies have reported cases with BML accompanied by multiple pleural and peritoneal nodules. In addition, the findings of recent cytogenetic studies are also consistent with a monoclonal origin of both uterine and pulmonary tumors [4, 27]. All of these studies indicate that pulmonary leiomyomatous nodules are metastatic. However, BML has been determined to be a benign lesion, because these tumors consist of well-differentiated, benign-appearing smooth muscle cells with a regular karyotype that lacks pleomorphism or mitotic figures. Additional investigations are necessary to determine the existence of primary pulmonary leiomyoma, because leiomyoma arising in men and children has been reported as non-metastatic, with residual alveoli in the lesions and no vascular tumor embolus in the lungs [27].

The diagnosis of BML can only be made with certainty after careful and extensive sampling of the primary uterine tumor to exclude small foci of sarcoma as well as sampling of the pulmonary tumor to rule out primary neoplasm. Even though it is biologically peculiar, BML should continue to be recognized as a distinct entity because current morphologic criteria do not allow primary uterine tumors to be classified as smooth muscle tumors of uncertain malignant potential even if they have metastasized to the lungs.

In summary, although BML is a rarely reported disease, women of reproductive age with a history of uterine leiomyoma, especially uterine tumor surgery, should be considered for possible diagnosis of pulmonary BML when solitary or multiple pulmonary nodules are present. A biopsy of multiple lesions should be taken to identify the pathological types and sources as soon as possible. If the pathological findings of the pulmonary nodules reveal a well-differentiated leiomyomatous tumor, careful examination of the uterus should be performed to identify the possible primary origin of the metastatic pulmonary lesions. Surgery is the first choice for patients who can tolerate the operation; if surgery is not a good choice, hormonal therapy may be the only effective treatment alternative, coupled with monitoring of the hormone levels and monitoring for relapse or distant metastasis of BML.

Disclosure of conflict of interest

None.

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